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A Report on the Implementation Aspects of the International Atomic Energy Agency's First Doctoral Coordinated Research Project, "Management of Liver Cancer Using Radionuclide Methods With Special Emphasis on Trans-Arterial Radio-Conjugate Therapy and Internal Dosimetry"

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Liver cancer is one of the most dreaded cancers, and it is highly prevalent in the developing countries, where the resources are extremely scarce to deal with this disease using the current commercially available and expensive therapeutic radiopharmaceuticals. The International Atomic Energy Agency (IAEA), in pursuit of its mandate to promote the application of nuclear technology in the health care in its Member States, has developed and clinically evaluated a new and cost-effective therapeutic radio-conjugate, rhenium-188 (^{188}Re)-lipiodol for the treatment of hepatocellular carcinoma through its first Doctoral Coordinated Research Project. The ready availability of no-carrier-added ^{188}Re from the tungsten-188/^{188}Re generator represents a potentially important source of a therapeutic radioisotope for a broad range of therapeutic applications in nuclear medicine. The alumina-based tungsten-188/^{188}Re generator system comes with reasonable cost and exhibits attractive therapeutic properties, excellent performance and very long useful shelf-life. Because of the long shelf-life of several months, the use of this generator offers a unique opportunity for the cost-effective and routine availability of a versatile therapeutic radioisotope on an on-demand basis. Further, using its extensive global network and outreach, the IAEA has also transferred the technology of the in-house preparation and use of ^{188}Re-labeled lipiodol to many institutions around the world, which can now prepare ^{188}Re-labeled lipiodol in their own radiopharmacy laboratories and treat patients. This effort of the IAEA in trying to address some of the challenges of liver cancer therapy in developing countries has been and truly a global venture with involvement and contributions from several organizations, institutions and numerous individuals. This article discusses some of the implementation aspects of this very important activity of the Agency.
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Hepatocellular carcinoma (HCC) is a malignant epithelial tumor arising from parenchyma liver cells. It is one of the world's most common malignancies, causing almost 1 million deaths annually. About 315,000 new cases of HCC are reported per year, which constitutes 5.6% of all cancers among men and 2.7% of all cancers among women. Control strategies to prevent occurrence of HCC are suboptimal, which is evident by the increasing incidence of HCC even in developed nations like the United States, where the prevalence of the disease is one of the lowest in the world.

Currently, patients with HCC have an extremely poor prognosis, with a 5-year survival rate of less than 5%. However, morbidity and mortality in such patients are not determined by the presence of HCC alone but are also influenced

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by the activity of the underlying liver disease, as well as the functional status of the liver. The stage of the tumor (size, number, vascular invasion, extra-hepatic spread) has been consistently documented to be an important determinant of the natural course of the disease. These factors are major variables that influence recent therapeutic strategies directed against this tumor. Therefore, therapy of HCC needs to be optimized depending on the foregoing factors which affect final outcome of the disease.

Various forms of therapies such as surgical resection, orthotopic liver transplantation, and induction of coagulative necrosis by percutaneous injection of agents such as ethanol, acetic acid, and hot saline or by application of microwaves or lasers have been used as radical, curative treatment of HCC. The understanding of the pathology, pathogenesis, natural course, and risk factors of HCC during the last 3 decades has resulted in the development of multiple therapeutic approaches with promising-yet-varying results.

Most patients with hepatoma at the time of presentation fall into the intermediate/inoperable category and, for such patients, radionuclide methods to deliver high radiation doses to the tumor must be considered. Uncontrolled studies using radioisotopes like ^{131}I, ^{90}Y, ^{166}Ho, and ^{186}Re conjugated to monoclonal antibodies, lipiodol, or chemical compounds have shown promising results. However, because of a lack of prospectively designed randomized trials, their efficacy is yet to be optimally evaluated. There has also been a report on the utility of radionuclide therapy as an adjuvant treatment after resection of "curable" HCC. It has been shown that patients given a single administration of 1 GBq of ^{131}I-lipiodol have significantly longer survival and fewer recurrences than those not treated. It is important that the results of this study be verified and confirmed by reproducing the results in a prospective trial.

It may be noted that the disease is most prevalent in those communities with the least resources for setting up clinical trials. Hence, the role of the international organizations like IAEA and the World Health Organization are extremely important in assisting them in setting up and coordinating such trials. Currently, the only commercially available radiopharmaceutical for the treatment of liver cancer, ^{131}I-lipiodol, is prohibitively expensive and therefore not practical to use on a routine basis in developing countries of the world. For nuclear medicine to develop a cost-effective therapeutic procedure and play a key role in the treatment of HCC, new methods must be developed, tested, and standardized in randomized controlled trials.

IAEA's Doctoral Coordinated Research Project on Liver Cancer

The Agency's efforts in developing and evaluating a new cost-effective therapeutic radiopharmaceutical for the treatment of HCC have been greatly appreciated by the global scientific community. The work related to the coordinated research project (CRP) was performed under the auspices of the Nuclear Medicine Subprogramme, Project No. F1.02: Radiopharmacology and therapeutic applications of unsealed radioactive sources in the management of thyroid cancer, liver cancer, joint diseases and coronary artery disease. The main objectives of the project were to develop, evaluate, and standardize new diagnostic and therapeutic radiopharmaceuticals and to establish effective use of appropriate in vivo therapeutic nuclear medicine procedures in the developing Member States through Agency support. The CRP on liver cancer was one of the several tasks performed under the project.

Objectives of the CRP

The specific objectives of the CRP were to develop a cost-effective radiopharmaceutical (^{188}Re-labeled lipiodol) for loco-regional therapy of nonoperable HCC; to determine its safety (Phase-I study); to determine its efficacy (Phase-II Study); to determine the overall response rate, progression-free, and overall survival ("utility") of loco-regional radiopharmaceutical therapy using ^{188}Re-lipiodol; to develop a strategy for the effective management of HCC; and to educate and train medical doctors, technologists, and scientists from the participating centers in the field of radionuclide therapy and to assist at least one professional from each participating center to obtain a PhD, MD, or equivalent postgraduate degree from the local universities.

The expected outputs included formation of a network of participating institutes to do research under the CRP, a ready-to-use standardized procedure for labeling ^{188}Re with lipiodol, treatment and dosimetry protocols for ^{188}Re-labeled lipiodol therapy, and a report on the safety and efficacy of ^{188}Re-labeled lipiodol therapy of HCC. The other expected outputs were publication of results in journals, presentation of the work at national and international scientific meetings and conferences, and conferring of PhD or equivalent degrees by the respective local universities to trainees from participating centers on the basis of their research work performed under the Doctoral CRP.

A number of activities were performed under the CRP, including a pre-CRP consultants' meeting, a technical cooperation mission, and a workshop. Tables 1 and 2 provide the list of activities performed under the CRP. Although the Doctoral CRP was an activity of the Division of Human Health performed under the regular-budget program of the IAEA, the overall implementation was done through an effective linking of the regular budget CRP activities with various national, regional and interregional projects of Agency's Department of Technical Cooperation.

Formation of Research Contract Holder and Research Agreement Holder Pairs and Registration of Doctoral Students at Their Local Institutions/Universities

A total of 8 Research Contracts, 8 Research Agreements, and 2 Technical Contracts were awarded under the CRP (Table 3). After taking into consideration the research preference of the

Table 1 Activities Carried Out Before the Start of the CRP as a Part of the Preparation for the CRP, Including Situation Analysis and Data Collection

Study No.	Type of Activity	Funding Provided by
1	**TC Mission to Vietnam, 1998:** Vietnam is one of the countries in Asia which has one of the maximum prevalences of liver cancer cases in the world. This technical mission was conducted to assess the actual ground situation in the country with regard to the overall management of liver cancer.	TC (VIE6020)
2	**CSM, Shanghai, China, April, 1999:** China has the highest incidence of liver cancer in the world. TC was requested to support a regional consultants meeting on liver cancer in China with participants from several Asian countries with high incidence of liver cancer. Subsequent to this CSM, Liver cancer was included as one of the themes of the ongoing thematic regional TC project in Nuclear Medicine.	TC (RAS6028)
3	**CSM, Vienna, December, 1999:** A group of consultants were invited to Vienna to draft the first protocols (dosimetry, radiopharmaceutical and clinical) for use in the CRP.	RB
4	**RTC, Singapore, February, 2000:** This was done as a part of the activity of the RCA Regional Thematic Technical Cooperation Project in Nuclear Medicine. All prospective participants of the Thematic CRP on Liver Cancer were invited to this training course.	TC (RAS6028)
5	RCC Approval of Thematic CRP, May, 2000	RB

TC, Department of Technical Cooperation, IAEA; RB, Regular Budget; CSM, Consultants Meeting; RTC, Regional Training Course.

participating centers, research partnerships were formed and research topics were assigned. It was in fact mandatory for all participating research contract institute to participate in patient treatment procedures and contribute to the clinical trial. A few centers performed additional research activities related to dosimetry (Colombia and Thailand) and radiopharmacy (Singapore) in collaboration with their research agreement holder counterparts.

Standardization of ^{188}Re-Lipiodol Labeling Procedure

The ready availability of no-carrier-added ^{188}Re from the tungsten-188/^{188}Re generator represents a potentially important source of a therapeutic radioisotope for a broad range of therapeutic applications in nuclear medicine, oncology, rheumatology and interventional cardiology. The alumina-based tungsten-188/^{188}Re generator system developed and provided by the Oak Ridge National Laboratory (ORNL) Nuclear Medicine Program exhibits excellent performance, very long useful shelf-life, reasonable costs, and the attractive therapeutic properties of ^{188}Re. Because of the long shelf-life of several months, use of this generator offers a unique opportunity for the cost effective routine availability of a versatile therapeutic radioisotope on an on-demand basis. Such availability is particularly important for isolated sites in developing regions. After taking into consideration several such aspects including cost, availability, ease of use, anticipated efficacy and practicality; the IAEA decided to use ^{188}Re as the radio isotope and develop the new radioconjugate ^{188}Re-lipiodol for the treatment of liver cancer.

Standardization of the labeling procedure of ^{188}Re with lipiodol was one of the first things to be accomplished under the project. Lipiodol is an iodinated and esterified lipid of poppy seed oil and has been in use as a contrast agent for detecting or treating liver cancer for several decades. It was decided to first adopt the technology of preparing the lipophilic ^{188}Re-labeled compound 2,2,9,9-tetramethyl-4,7-diaza-1,10-decanedithiol, developed by Prof. Jeong at the Seoul National University, for use in the CRP. Further improvements were also accomplished by Prof. Jeong in the labeling procedure to achieve improved retention of the radio-conjugate in liver cancer cells. The improved version of the compound 4-hexadecyl-2,2,9,9-tetramethyl-4,7-diaza-1,10-decanedithiol (HDD) was finally approved for use at the participating centers of the CRP. The HDD ^{188}Re radiolabeling method was established at Seoul National University and was successfully formulated into a kit form before the start of the CRP in the year 2001. More than 800 kits were provided to the CRP participants in Australia, China, Colombia, India, Mongolia, Philippines, Singapore, Thailand, and Vietnam. Details of issues associated with the use of the tungsten-188/^{188}Re Generator and Concentrator System and Preparation of ^{188}Re HDD kits are given in another article elsewhere in this issue.

Supply of Rhenium Generators to Participating Centers

At the beginning of the CRP the Agency sealed an agreement with the U.S. Department of Energy to procure rhenium generators at a significantly subsidized price. The Department of Energy also agreed to provide necessary technical assistance in setting up of rhenium generators at various research sites in the Member States, including fabrication and supply of a few accessories like rhenium shielding devices. Each partic-

Table 2 Major Activities Carried Out During the Active CRP From 2000 to 2004

Type of Activity	Funding Provided by
AGM on Thematic CRP, Vienna, November 2000	RB
First Research Coordination Meeting, Singapore, December 2000	RB
Regional Training Course on Liver Cancer, Perth, Australia, April 2001	TC (RAS6028)
National Workshop on Radionuclide Treatment of Liver Cancer, Singapore General Hospital, Singapore, August 2001	TC (RAS6028)
National Workshop on Re-188 Lipiodol Therapy–As a part of the Phase-1 study, Vietnam (combined with a RTC for NM technologists), October 2001	TC (RAS6028 & VIE6022)
National Workshop on Radionuclide Treatment of Liver Cancer, Bogota, Colombia, October 2001	TC (COL0010)
National Workshop on Radionuclide Treatment of Liver Cancer, Ulaanbaatar, Mongolia, March 2002	TC (MON6008)
Mini RCM, Beijing (in conjunction with the IAEA Symposium on Cardiovascular Nuclear Medicine, May 2002)	RB
Fellowship Training of the PhD students from Vietnam, Philippines, Mongolia, Thailand, Singapore, Colombia (training provided in France, Singapore, USA and UK)	National, regional TC projects. Human resources development projects etc.
Expert missions to participating sites: Several expert missions fielded to participating sites in Vietnam, Mongolia, Singapore, Colombia, Thailand, Philippines, India etc.	National, regional TC projects. Human resources development projects etc.
Regional Workshop on Liver Cancer; Ho Chi Minh City, Vietnam, 2002	TC (RAS6028, VIE6022+ INT0060
National Workshop on Liver Cancer in Philippines in conjunction with the Regional Training Course on Nuclear Oncology, August 2002	TC (RAS6028)
National Workshop on Liver Cancer Treatment, Bangkok, Thailand, 2003	TC (HRD Project)
Fabrication of Rhenium Concentrator Shielding Device	RB (DOE-USA)
Creation of a new regional project in the RCA region on Radionuclide Treatment Liver Cancer (2003-2006)	TC
National Project Coordinators' Meeting, Penang, 2003	TC
Regional training course and workshop on Interventional Nuclear Medicine with special emphasis on trans-arterial radioconjugate therapy of HCC, New Delhi, India, 2003	TC
Liver Cancer National Workshop, Manila, Philippines, 2003	TC
Second RCM of the CRP, New Delhi, India, December 2003	RB
TC mission to Vietnam to evaluate the progress in work related to liver cancer projects, April 2004	TC-VIE6022

ipating center of the CRP received a minimum of 4 to 5 rhenium generators during the active CRP period. Besides using the funds from the regular budget, funds from IAEA's various national, regional and Interregional technical cooperation projects were also used to procure and supply rhenium generators to the participating centers.

Standardization of Dosimetry Protocol

Like the radiopharmaceutical labeling protocol, which was developed before the start of the actual clinical trial, a dosimetry protocol was also developed at one of the Research Agreement Holder institutes, Memorial Sloan Kettering Cancer Center, New York by Dr. Pat Zanzonico. The dosimetry protocol was designed with a view to standardize dose calculation and provide maximum tolerated dose (MTD) to each individual patient, which would not deliver more than 1.5 Gy to marrow, 30 Gy to liver or 12 Gy to the Lungs. An Excel spreadsheet (Microsoft, Redmond, WA), with the necessary reference data, has been prepared to perform and automate the calculations of MTD. (A copy of this spreadsheet can be obtained free of charge from either the corresponding author or Pat Zanzonico [zanzonip@mskcc.org].) Details of dosimetric considerations are given in another chapter elsewhere in this supplement.

Clinical Protocol

A Consultants' Meeting in Vienna prepared the first draft of the clinical protocol in November 1999, which was circulated among the prospective participants of the CRP, who were invited to a Regional Training Course/Workshop on Liver Cancer in Singapore in February 2000. In fact this workshop was used to screen the candidates for the Doctoral CRP. Based on the inputs received from the participants of the regional training course the clinical protocol was suitably modified and included in the CRP proposal submitted to IAEA's Research Contract Committee (RCC) for approval. The thematic CRP was formally approved by the RCC in May 2000. The first research coordination meeting was held in Singapore in December 2000. The first RCM finalized the

Table 3 Names of the Research Contract and Research Agreement Holder Pairs Along With the PhD Scholars Doing Research Under the Thematic CRP

Study No.	Name of Research Contract Holder (Country)	Name of Research Agreement Holder (Country)	Name of the PhD Scholar	Affiliated University/ Institute	Theme of PhD Work
1	R. Esguerra (Colombia)	C. Divgi (USA)	1. P. Bernal 2. M. Osorio	Fundacion Santa fe de Bogota	Clinical trial, dosimetry
2	S.L. Chen (China)	F.F. Knapp (USA)	1. Xiaoyun Gu 2. Yancheng Chen	Shanghai Second University, Shanghai	Clinical, rhenium chemistry
3	P. Onkhuudai (Mongolia)	J. Buscombe (UK)	C. Sereegotov	Nacional Medical University of Mongolia	Clinical trial
4	D. Srivastava (India)	S.K. Acharya (India)	A. Kumar	All India Institute of Medical Sciences	Clinical trial
5	O. Monzon & S. Ang (Philippines)	J-L Raoul (France)	R. V. Ogbac	St. Luke's Medical Center	Clinical trial
6	Felix X. Sundram (Singapore)	J-M Jeong (Korea)	M.M. Saw	Singapore National University	Radiopharmacy and clinical trial
7	P. Pusuwan (Thailand)	C. Divgi (USA)	K. Prabhasavat	Mahidol University	Dosimetry, clinical trial
8	T. Chau (Vietnam)	J.H. Turner (Australia)	No student	Cho Ray Hospital, HCMC	Clinical trial

research contract holder and research agreement holder pairs, approved the candidature of the PhD scholars and allocated the research work to be carried at each individual center depending on their preference, available infrastructure and capabilities (Table 3).

Preparatory Work at the Participating Centers

All participants went to their respective institutions from the first RCM in Singapore with the final agreed protocols. Under the research contract, it was mandatory for each participating center to get the approval of their respective institutional ethics committees for the use of ^{188}Re-lipiodol in the treatment of inoperable HCC. Besides this, each participating center was also required to fulfill all license requirements (with regard to radiation safety, infrastructure and personnel) for obtaining, installing and handling at least one 2-Ci tungsten-rhenium generator at any given time in a year.

It was indeed extremely satisfying to see that all participating centers were able to fulfill IAEA's as well as DOE's (Department of Energy, Washington, DC) requirements for supply and delivery of rhenium generators from ORNL (Oak Ridge, TN).

By March 2001, the clinical and dosimetry protocols as well as necessary administrative procedures for supply of rhenium generators to participating centers were all completed. However, the actual treatment of patients with ^{188}Re-labeled lipiodol could not be started at any one of the participating centers. The main reason for this was lack of experience and confidence on the part of most participants to apply the complicated dosimetry protocol and initiate the rather invasive radionuclide therapeutic procedure, which required trans-arterial catheterization of hepatic artery. At this point in time, the IAEA realized the difficulty in the implementation of the project and tried to play a real proactive role in the implementation of the CRP with active help and collaboration of the department of technical cooperation.

At first, it was decided to organize a regional training course and workshop on liver cancer at Perth, Australia, with special emphasis on dosimetry. All participants of the CRP from the Asia region were invited to this workshop using the funds from the RCA Regional project on health care, whereas participants outside of the Asia region were invited using the funds from one of IAEA's Interregional projects. Experts from Memorial Sloan Kettering Cancer Center and Fremantle Hospital conducted dosimetry workshops where each participant was trained on the actual procedure and taught how to use the Excel spreadsheet and calculate MTD. At this workshop one CD ROM was also produced demonstrating various steps of rhenium elution and Lipiodol labeling.

Subsequent to the Perth training course and workshop, the Agency organized four national workshops at 4 participating centers of the CRP, namely Singapore, Vietnam, Colombia and Mongolia. With the help and collaboration of the department of technical cooperation the Agency fielded several expert missions to conduct these national workshops, during which actual patient treatment procedures were performed. In fact these were done as a part of the Phase-I study of the clinical (therapeutic) trial.

Clinical Trial: Phase I Study

The Phase I study to determine the safety of trans-arterial ^{188}Re-labeled lipiodol in the treatment of patients with inoperable HCC was conducted at few selected sites, including Vietnam, Colombia, and Singapore. The ^{188}Re-labeled lipiodol conjugate was prepared by the local Radiopharmacists

using an HDD kit from Korea and Lipiodol purchased from local markets. Fifteen patients received one treatment of radioconjugate. The amount of radioconjugate to be administered was determined based on radiation absorbed dose to critical normal organs, calculated following a "scout" dose of radioconjugate. The organs at greatest risk for radiation toxicity are the normal liver, the lung, and the bone marrow. As described previously, in all patients the specially designed Excel spreadsheet was used to determine MTD, ie, the amount of radioactivity calculated to deliver no more than 12 Gray (Gy) to lungs, or 30 Gy to liver, or 1.5 Gy to bone marrow. These doses have been found to be safe in multiple previous trials using external beam therapy and systemically administered radiopharmaceuticals. All patients were followed for at least 8 weeks after therapy, until recovery from all toxicity. Parameters evaluated included toxicity, response as determined by contrast-enhanced computed tomography, palliation of symptoms and overall survival at 6 months, and quality-of-life parameters, including performance status (Karnofsky) and hepatic function (Child's classification). All patients had both the "scout" dose and the treatment dose. In the majority of patients, from the "scout" dose studies, the radiation absorbed dose to normal liver (followed by lungs) was the most common limiting factor to the treatment dose. In other words, the MTD was decided in most cases by radiation dose to liver, or by dose to lung. Radiation dose to bone-marrow was negligible and was thus not a factor for MTD calculations. Side-effects were minimal, usually right hypochondrial discomfort and low-grade fever. Liver function tests at 24 hours and 72 hours showed no significant changes and full blood counts at one week, four weeks and 12 weeks showed no changes (no bone-marrow suppression). Based on the Phase 1 results ^{188}Re-labeled lipiodol was cleared as a safe and cost-effective method to treat primary HCC via the trans-arterial route. Details of the toxicity study are given in the main clinical paper which appears elsewhere in this supplement.

Phase II Study

In the Phase II efficacy study 185 patients were treated with ^{188}Re-labeled lipiodol. The level of radioconjugate administered was based on radiation absorbed dose to critical normal organs, calculated following a "scout" dose of radio-conjugate. The dosimetry Excel spreadsheet, as described before, was used to determine maximum tolerated activity. A single treatment was given to 134 patients, 42 patients received 2 doses, 8 received 3, and 1 patient received 4 treatments. The total injected activity, including the scout dose during the first treatment, ranged from 2l to 364 mCi (mean, 108 mCi). Patients were followed for at least l2 weeks after therapy. The clinical parameters evaluated included toxicity, response as determined objectively by contrast-enhanced computed tomography, palliation of symptoms, overall survival, performance status (Karnofsky), and hepatic function (Child's classification). Liver function tests, serum alpha-fetoprotein levels and complete blood counts were done at each follow-up visit. Side effects were minimal and usually presented as loss of appetite, right hypochondrial discomfort, and low-grade fever. Liver function tests at 24 and 72 hours showed no significant changes, and complete blood counts at 1 week, 4 weeks, and 12 weeks showed no changes (no bone marrow suppression). Data on largest tumor diameter after therapy and/or tumor response as evaluated from CT scans are available for 88 patients. Complete disappearance of tumor was recorded in 3 (3%) patients, partial response in 19 (22%), stable disease in 41 (53%), and tumor progression in 19 (22%) patients. Estimated 3-, 6-, 9-, 12-, and 24-month survival was 93%, 60%, 46%, and 23%, respectively. Median follow-up was 455 days. The results of this multicenter study show that ^{188}Re lipiodol is a safe and cost-effective method to treat primary HCC. Details of the Phase II study are enumerated in another section published elsewhere in this issue.

Awarding of PhD Degrees Under the CRP

A total of 9 students were initially registered for PhD or equivalent postgraduate courses at the beginning of the CRP. A list of students registered and their local (Research Contract Holder) and distant (Research agreement Holder) supervisors are given in Table 3. As per the latest information, 5 researchers have already received their PhD Degrees under the Thematic CRP:

1. Dr. Maung Maung Saw, National Singapore University, Singapore (2005)
2. Dr. Ajay Kumar, AIIMS, New Delhi, India (2006)
3. Dr. Xiaoyun Gu, Shanghai Second University, Shanghai, China (2004)
4. Dr. Yancheng Chen, Shanghai Second University, Shanghai, China (2004)
5. Dr. C. Sereegotov, National Medical University of Mongolia, Ulaanbaatar, Mongolia (2007)

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Scientific Presentations at National and International Conferences

Results of the various aspects of the CRP have been presented at a number of national, regional, and international conferences. These include:

1. World Congress, WFNM&B, 2002 (Santiago, Chile)
2. EANM, Vienna, 2002
3. SNM, Annual Meeting, New Orleans, USA, 2003
4. EANM, Amsterdam, 2003
5. Colombian Association of Nuclear Medicine Congress, Cali, Colombia, 2003
6. ARCCNM, Annual Convention, Dhaka, Bangladesh, 2003
7. IAEA International Symposium on Nuclear Oncology, 2004 to 05-13
8. Rajiv Gandhi Institute International Conference on Cancer, Delhi, India, 2004 to 05-13
9. SNM Annual Meeting, Philadelphia, USA, 2004

10. First International Conference on Radiopharmaceutical Therapy (ICRT-2005), Limassol, Cyprus, 2005

Fabrications

A rhenium shielding device was fabricated in collaboration with ORNL through an IAEA Technical Contract.

Overall Assessment of Progress Toward Achieving Objectives

The CRP started in the middle of the year 2000, as the first Doctoral CRP of IAEA combining research and development activity of the IAEA with the higher education programs of the participating universities in the Member States. Besides developing a new cost-effective therapeutic radiopharmaceutical for treating HCC, and assessing its safety and efficacy; the second major objective of the CRP was to develop human resources in the field of radionuclide therapy through establishment of a link between the CRP activities of IAEA and the postgraduate medical education and training programs in the IAEA Member States. The CRP has achieved several of its objectives, namely; development of Re-188 Lipiodol and standardization of the labeling procedure, development of ^{188}Re-labeled lipiodol internal dosimetry protocol, evaluation of its safety for use on humans (Phase 1 study), evaluation of its efficacy in the treatment of HCC, producing at least one PhD thesis per participating institute during the period of the CRP.

The agency's efforts in addressing some of the challenges of liver cancer in developing countries is a truly global effort with the following principal players: (1) IAEA: NAHU-NMS, which is responsible for coordination of the entire research and developmental activities, protocols and multi-center studies; (2) IAEA: Department of Technical Cooperation, which is responsible for the transfer of technology, human resources development, fellowship training, group training, expert services, and supply of radiopharmaceuticals; (3) Department of Energy, Washington, DC, which is responsible for the supply of ^{188}Re generators at a subsidized price to IAEA (U.S. $7,800 instead of 14,000), expert advice, fabrication of accessories etc.; (4) Memorial Sloan Kettering Cancer Center, New York, which is responsible for developing the clinical and dosimetry protocols; (5) Seoul National University Hospital, which is responsible for developing the ^{188}Re-labeled lipiodol; (6) Centre Eugene Marquis, Rue de la Bataille Frandres-Dunkerque, Rennes-Cedex, France, which is responsible for clinical protocols; (7) Singapore General Hospital, which acts as the core center for the clinical studies and 10 centers from 10 developing countries, 6 centers from 5 developed countries, and 9 universities from 9 developing countries, making it a truly global venture.